FRONTIER

Revolution in the diagnosis and management of hepatitis C virus infection in current era

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Abstract

Chronic hepatitis C virus (HCV) infection is a major global public health problem, particularly in developing part of the world. Significant advances have been made in the early diagnosis and treatment of the disease. Its management has been particularly revolutionized during the past two decades. In this review, we summarize the major advances in the diagnostic and management armamentarium for chronic HCV infection. The focus of the present review is on the newer directly acting anti-viral agents, which have revolutionized the management of chronic HCV infection. Management of uncomplicated chronic HCV infection and of specific complications and special at-risk populations of patients will be covered in detail. Despite the advent and approval of highly effective and well tolerable oral agents, still many challenges remain, particularly the affordability, the equitable distribution and access to later drugs. The World Health Organization aims to eliminate viral hepatitis including HCV by 2030 since its poses a major public health threat. There is an urgent need to ensure uniform and early access to diagnostic and therapeutic facilities throughout the world if the later goal has to be realized.

Key Words: Hepatitis C virus; Interferons; Diagnosis; Management; Directly acting anti-viral agents

Core Tip: Chronic hepatitis C virus (HCV) infection is a major public health threat worldwide, particularly in resource-constrained countries. Although significant advances have been made in the early diagnosis and treatment of the disease, many unmet challenges remain to be tackled, particularly the affordability, equitable distribution and access to these methods. The World Health Organization aims to eliminate viral hepatitis including HCV by 2030. This frontier article addresses the burden of chronic HCV infection, delineates the current therapeutic options, and identifies future strategies to tackle this highly prevalent disease.

INTRODUCTION

Hepatitis C virus (HCV) accounts for majority of viral hepatitis-related mortality per annum worldwide [1]. Chronic HCV infection persisting for more than 20-30 years causes liver cirrhosis and/or hepato-cellular carcinoma (HCC). World Health Organization (WHO) estimates that around 71 million people are suffering from chronic HCV infection with highest incidence in WHO Eastern Mediterranean and European Regions[2]. Globally, around 400000 people die annually due to chronic HCV-associated complications, predominantly as a result of decompensated hepatic cirrhosis or development of HCC. The economic impact of the disease is also enormous, particularly for emerging economies. HCV virus has greater genetic diversity than HBV or human immunodeficiency virus (HIV). HCV has seven genotypes with around 67 subtypes[3]. Spectacular advances have been made in the scientific field in the diagnosis and management of this infection in the past few years. Still, ironically, fewer than 20% of those living with HCV infection globally are aware of their disease, and the immediate challenge is to engage, screen, diagnose and treat everyone in whom treatment is warranted. These undiagnosed HCV cases worldwide represent an important hurdle to achieve the WHO goal of HCV elimination by 2030. Many social, access to healthcare and economic hurdles remain in the path to HCV elimination. However, many success stories are being reported from many high prevalence countries, including Egypt[4]. It is beyond the scope of this review article to cover all aspects of HCV infection; hence, the focus of this review is on the remarkable advances that have taken place in the diagnosis and management of chronic HCV infection, particularly in vulnerable and "difficult-to-treat" groups and on strategies being implemented to eliminate HCV infection.

DISCOVERY OF HEPATITIS C VIRUS

The story of discovery of HCV is unique in that it was identified by non-conventional means, i.e., molecular biologic techniques rather than direct visualization and cell culture. It is pertinent to briefly revisit this story here to better understand the advances that have taken place in the diagnostic and therapeutic aspects of HCV infection. It all started with the finding a new type of hepatitis in patients who received blood transfusion in early 1970s. As hepatitis A virus and hepatitis B virus (HBV) were not present in such patients, Alter and co-workers in 1975 coined the term "non-A, non-B (NANB) hepatitis" for this type of hepatitis. They collected plasma/serum samples from a blood donor with chronic hepatitis and four people who developed "NANB hepatitis" after receiving blood transfusion, and injected these samples into five chimpanzees. All five chimpanzees developed hepatitis, as evidenced by rise of serum alanine aminotransferase levels as well as liver pathological changes, confirming the presence of a yet unknown transmissible agent in the blood of patients with NANB hepatitis. In 1989, Houghton and co-workers constructed a random-primed complementary DNA (cDNA) library using plasma samples from patients with NANB hepatitis. One clone in this library was not derived from host DNA, and appeared to be from a novel RNA virus belonging to the *Flavivirus* family (at least 10000 nucleotides and positive-stranded). They named this novel virus as HCV. Later on, Rice and co-workers constructed a full-length clone of HCV cDNA that was able to be transcribed to an infectious RNA variant of HCV. Upon intrahepatic inoculation of this clone, chimpanzees developed chronic hepatitis, with production of antibodies against HCV and viral replication in the blood. Subsequently, Bartenschlager and co-workers developed an *in vitro* cell culture using a human hepatoma cell line to replicate HCV. This cell-based model was indispensable in highlighting the biological features of HCV as well as developing anti-HCV agents. The 2020 Nobel Prize in Physiology or Medicine was awarded to Drs. Harvey J. Alter, Michael Houghton and Charles M. Rice for the discovery of HCV[5].

HCV DIAGNOSTICS

An accurate diagnosis and linkage to care is the key to successful treatment and ultimately eradication of any infectious disease. HCV infection is no exception to this rule. Hence, simple, affordable, rapid and high quality diagnostic tests of active infection at the point-of-care (POC) are central to the achievement of HCV elimination goal. While the world has focused its attention over the last decade on the final stages within the cascade of care to develop and increase access to directly acting antiviral agents (DAAs), relatively less attention has been paid to ensure accurate and affordable diagnostic tools to make wide-scale global treatment a reality. The diagnostic armamentarium for HCV infection principally comprises of two approaches: detection of antibodies against the virus in the serum and HCV PCR, the later being the gold standard. More recently, HCV antigen test has also been introduced as an alternative to HCV PCR. Each of the tests has merits and demerits. Ironically, in many settings, prohibitively high costs of HCV diagnostics often now exceed the cost of curative therapy. Thus, improving access to rapid, simple, and affordable HCV diagnostics is critical to achieve global HCV elimination and should be considered a public health priority.

Simplified diagnostic solutions

American Association for the Study of Liver Diseases (AASLD) recommends all individuals above 18 years to be screened for HCV for at least one-time owing to treatment benefits and reduction of morbidity and mortality. HCV-antibody tests approved by US Food and Drug Administration (FDA) should be utilized for screening of HCV infection. To detect active viremia and for treatment decisions, HCV RNA with a detection limit of ≤ 25 IU/mL is advised. However, immunocompromised populations or patients exposed to HCV within 6 mo should undergo HCV RNA testing despite negative HCV antibody test. A simple and updated HCV testing algorithm recommended by Center for Disease Control is shown in Figure 1. Such simplification of current hepatitis C diagnostic algorithms and the advent of digital diagnostic devices will play a pivotal role in achieving the WHO's target goals of hepatitis C elimination by 2030. Over the last decade or so, hepatitis C diagnostics have been revolutionized by the introduction and commissioning of state-of-the-art HCV diagnostic platforms which have been efficiently applied in high-risk HCV populations in developed countries as well as in some low-to-middle income countries (LMICs) to diagnose millions of undiagnosed hepatitis C-infected people. POC rapid diagnostic tests (POC-RDTs), reflexive RNA testing, dried blood spot sample analysis and hepatitis C self-test assays have demonstrated their diagnostic value in real-world clinical experiences, in mass hepatitis C screening campaigns, and disenfranchised native hepatitis C populations in remote areas[6].

HISTORY OF DISCOVERY OF HCV TREATMENT

The development of successful antiviral chemotherapeutic agents lagged behind the antibiotics and has primarily evolved in past 50 years[7]. This developmental delay has as its cause many hurdles like the delays in the advent of culture system, experimental animal models and a standard method for antiviral drug formulation. Moreover, the challenges encountered in developing a targeted therapy for a specific viral agent included drug toxicity, viral genetic variability and resistance profile, all these lengthened its developmental process[7].

HCV-specific antiviral agents met the same development delay. The discovery of HCV began from 1975 with the identification of new transfusion-related "NANB" hepatitis virus to the isolation of a single cDNA clone named HCV in 1989[5,8-10]. The successful pilot study on NANBH, by Hoofnagle *et al*[11], in 1986 formed the basis of two randomized trials. Both trials demonstrated on-treatment effectiveness of interferon (IFN) alpha-b in HCV eradication[12]. Thus, in 1991, US FDA approved IFN-alpha for the treatment of chronic HCV infection. Later on, ribavirin (RBV), an oral nucleoside analogue, was utilized as a monotherapy for HCV infection. Due to transient antiviral effect of RBV, the focus of clinical trials shifted to combination therapy[9,12].

By increasing the treatment duration and with the addition of IFN-alpha with RBV, the sustained virological response (SVR) rate escalated from 6% to 42%[13]. However, this treatment option had many caveats, mainly the IFN-associated side effects and intolerability, which were later improved with the advent of once weekly pegylated IFN (PegIFN). Moreover, with the encouraging response in HCV genotypes 2 and 3, having an SVR rate of 70% to 80%, the combination of PegIFN with RBV, thus became the standard of care[12,14]. Although the "golden era of IFN" persisted for over a decade but the large cohort of patients having decompensated chronic liver disease, hemoglobinopathies, pregnancy and organ transplants were deprived of its treatment benefit[6,15].
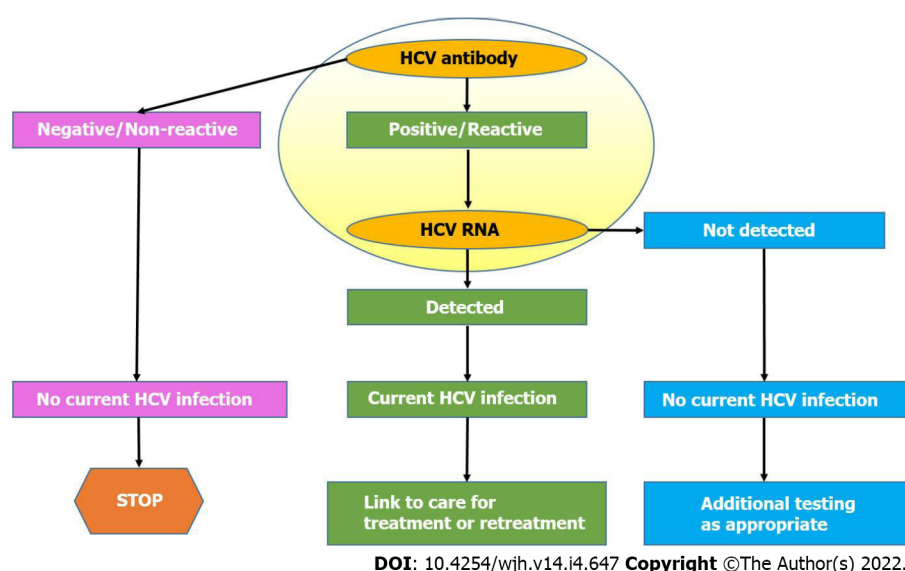
Figure 1 Center for disease control recommended sequence of testing for the diagnosis of active hepatitis C virus infection with some conditions in certain situations (not detailed). HCV: Hepatitis C virus.

DAAs

Later on, with the advancement in the molecular virology of HCV and the unraveling of HCV life cycle, three dimensional structure of HCV and its enzymes, led to development of the first generation of NS3-4A protease inhibitors: namely telaprevir and boceprevir[6]. These agents were only approved for treatment of chronic HCV genotype 1 patients in combination with PegIFN and RBV[12]. Due to their unfavorable pharmokinetics, drug- drug interactions, adverse effects and efficacy only for genotype 1, these agents were eventually replaced by second generation directly acting antiviral agents (DAAs); the early agent, simeprevir (SMV), in combination with PegIFN and RBV was effective against only genotypes 1, 2 and 4[16]. It was sofosbuvir (SOF), NS5A polymerase inhibitor, which led to a paradigm shift in the treatment cascade of HCV[6,9]. The discovery of SOF was not only a breakthrough in the advent of all-oral DAAs but was a beacon of light for dealing with the HCV infection in cirrhotics. Figure 2 depicts a simplified classification and major sites of action of various DAAs.

Initially, SOF was used in combination with PegIFN and RBV and was approved for genotypes 1 to 4. Cumulative SVR of various trials documented 87.6%, 95.6%, 91.3% and 92.3% in genotypes 1, 2, 3 and 4, respectively. Phase 4 TARGET trial documented effectiveness of SOF and RBV combination for 12 wk. The trial reported 91.9% and 75% SVR12 in non-cirrhotic population while 71.9% and 55.3% in cirrhotics treatment-naïve population with genotype 2 and genotype 3, respectively[17]. Moreover, ASTRAL 2 and ASTRAL 3 trials reported 80.4% and 73% SVR for HCV infection amongst the non-cirrhotic and cirrhotic populations treated with SOF and RBV combination for 24 wk[18].

In 2014, SOF with ledipasvir (LDV), a single pill combination, was approved for genotypes 1, 4, 5 and 6. ION-1 and ION-2 trials documented high efficacy of SOF/LDV combination in naïve and treatment-experienced population. Additionally, the use of RBV or treatment extension to 24 wk did not provide any significant benefit[19,20]. The pooled SVR12 of various trials was 92.2% and 96.1% in genotype 1 infected patients with and without cirrhosis[17].

Later in the same year, triple DAAs fixed dose combination was approved for genotype 1. The paritaprevir, ombitasvir, ritonavir combination with dasabuvir (PrOD) was evaluated in various trials with or without RBV for 12 wk. The combination showed more than 90% SVR12 in both cirrhotic and non-cirrhotic genotype 1 patients[17]. However, the risk of hepatotoxicity precluded its use in decompensated cirrhosis[4].

The usage of these initial DAAs made the least responsive genotype, genotype 1, safely and effectively treatable as opposed to what was seen with IFN, while genotype 3 became the "difficult to treat" genotype[21]. This scenario was dealt with by NS-5A replication complex inhibitor, daclatasvir (DAC). ALLY-3, a phase III trial included treatment naïve and experienced HCV populations with genotype 3. The trial documented overall 96% SVR12 with 12-week therapy of SOF and DAC combination but with sub-optimum response in cirrhotic patients[22]. However, ALLY-3+ study evaluated response of SOF, DAC and RBV combination for 12 and 16 wk in HCV genotype 3 patients with fibrosis stage > 3. The authors reported 100% SVR 12 in patients with fibrosis stage 4, while 86% in patients with compensated cirrhosis. Moreover, the trial also concluded comparable SVR 12 in 12- and 16-wk groups[23].
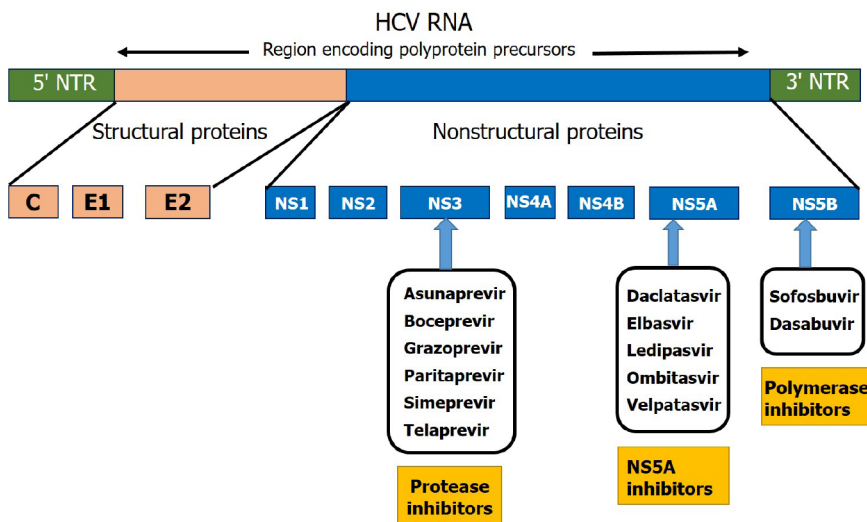
Figure 2 Mechanisms of action and main classes of direct-acting antivirals.

ASTRAL 3 study compared the response of 12-wk SOF/Velpatasvir (VEL) with 24-wk SOF with RBV combination in genotype 3 HCV infected patients. In this study population, overall SVR12 rate was statistically significantly higher in SOF/ VEL group (95%) than SOF RBV group (80%) [$P < 0.001$]. Moreover, in the SOF/VEL group with cirrhosis, 93% SVR12 was achieved in treatment-naïve group and 89% in experienced group with no discontinuation of treatment due to adverse effects[18].

Both the EASL and AASLD have recommended a shorter duration of therapy with the DAAs (8-12 wk) for non-cirrhotics and 12 wk for the cirrhotic patients[24,25].

The POLARIS 2 and 3 trials, which were phase III trials, compared 8 wk of SOF-VEL-voxilaprevir (VOX) with 12 wk SOF-VEL combination in cirrhotic and non-cirrhotic HCV population. POLARIS-2 study group excluded genotype 3 and documented non-inferior 95% SVR12 with SOF-VEL-VOX while SOF-VEL combination showed SVR 12 of 98%. However, the lower efficacy was attributed to higher relapse rate in genotype 1a population. POLARIS 3 trial documented similar efficacy of both regimens in HCV genotype 3 patients with compensated cirrhosis[25].

Thus, it has become possible to treat HCV infection even in the presence of decompensated cirrhosis, which was otherwise quite cumbersome during the IFN era. ASTRAL-4 trial documented response to SOF/VEL with or without RBV in decompensated liver disease. Therapy was associated with improved disease severity as documented by Model for End-stage Liver Disease (MELD) and Child Turcotte Pugh (CTP) scores. The study documented 83% and 86% overall SVR 12 with SOF/VEL for 12 and 24 wk, respectively. Moreover, 94% SVR12 was observed with SOF/VEL for 12 wk with RBV combination. However, study was not powered to detect significant difference between regimens[26]. Moreover, since the HCV protease inhibitors undergo hepatic elimination, many regimens that contain these agents are not recommended in patients with decompensated cirrhosis. FDA has received rare reports of worsening liver function or liver failure when these patients are treated with the following drugs: Elbasvir/grazoprevir (ELB-GRA); glecaprevir/pibrentasvir (GLE-PIB); SOF-VEL-VOX; and PrOD. Hence, these drugs should not be prescribed in patients with a history of prior hepatic decompensation [27].

The treatment of decompensated HCV-associated cirrhosis with DAAs has shown to cause an improvement in CTP as well as MELD scores. The TOSCAR study in which patients with MELD 15 or more were treated with SOF/DAC for 24 wk, showed that three fourth of the patients who achieved SVR had their median MELD and CTP scores decreased by two points[28]. Furthermore, an Italian multicenter study, showed a significant increase in the rate of switch to CTP A, at 24 wk post-SVR[29]. The improvement in the CTP and MELD scores has also been shown to result in the delisting of patients who were earlier candidates for liver transplantation[30,31].

Table 1 depicts the summary of the main trials of various DAAs in the treatment of chronic HCV infection.

HCV IN CHILDREN

It is estimated that 3.26 to 5.0 million children and adolescents worldwide have chronic HCV infection. To date, the global response has focused mainly on the adult population, but DAA regimens are now approved for children aged ≥ 3 years. Transmission routes, disease progression and treatment

Table 1 Summary of the main trials of various directly acting antivirals in the treatment of chronic hepatitis C virus infection

Trial Names	Regimens	Treatment experienced /naive	Genotype	Duration	Cirrhotics/non-cirrhotics	SVR12, %
TARGET	Sofosbuvir-Ribavirin	Naïve	2	12 wk	Cirrhotics	91.9
					Non-cirrhotics	71.9
			3		Cirrhotics	75
					Non-cirrhotics	55.3
ASTRAL 2 and ASTRAL 3	Sofosbuvir-Ribavirin	Naïve	3	24 wk	Cirrhotics	73.3
					Non-cirrhotics	90.4
ION 1	Sofosbuvir-Ledipasvir	Naïve	1	24 wk	Cirrhotics	96.9
					Non-cirrhotics	99.5
TURQUOISE-III	Ombitasvir-Paritasprevir-Ritonavir	Naïve	1b	12 wk	Cirrhotics	100
ASTRAL 3	Sofosbuvir- Velpatasvir	Naïve	3	12 wk	Cirrhotics	93
					Non-cirrhotics	98.2
		Treatment Experienced		12 wk	Cirrhotics	89.2
					Non-cirrhotics	91.2
ASTRAL 4	Sofosbuvir- Velpatasvir-Ribavarin	Naïve	1	12 wk	Cirrhotics	94.4
		Treatment Experienced				90
ASTRAL 4	Sofosbuvir- Velpatasvir-Ribavarin	Naïve	3	12 wk	Cirrhotics	84.6
		Treatment Experienced				96.2
POLARIS 2	Sofosbuvir-Velpatasvir-Voxilaprevir	Naïve	1-6	8 wk	Cirrhotics	91
					Non-cirrhotics	96
POLARIS 3	Sofosbuvir-Velpatasvir-Voxilaprevir	Naïve	3	8 wk	Cirrhotics	96.3
		Treatment Experienced				97

indications in children differ from those in adults. Globally, vertical transmission accounts for most HCV infections in the pediatric population, but transmission also occurs through unsafe medical interventions, especially in LMICs. Adolescents may acquire infection through injection drug use (IDU), and high-risk sexual practices especially among men who have sex with men (MSM). Although the occurrence of severe disease or cirrhosis in children is low at 2%, progression of liver disease can occur in childhood, and can impact quality of life. Early diagnosis can help timely access to treatment and prevention of long-term morbidity.

There are significant gaps in policies for HCV-infected children and adolescents. Many countries have no national guidance on HCV testing and treatment in children and adolescents. There is an urgent need for advocacy and updated policies and guidelines specific for children and adolescents. According to the joint recommendation by the AASLD and IDSA, children born to HCV infective mothers should be first checked with anti-HCV antibody at 18 mo followed by checking of HCV RNA at 3 years of age to confirm the diagnosis. DAAS are recommended in children aged 3 years and above[25].

HCV in oncology patients

Chronic HCV infection is a significant problem in patients with various types of cancer. The prevalence of chronic HCV infection among patients with cancer in the United States has been estimated to range from 1.5% to 10.6%, but this range may be an underestimate because many cancer centers do not routinely screen patients for HCV. The impact of chronic HCV infection on cancer management can be profound but can be mitigated through early diagnosis and treatment. Early diagnosis of HCV infection and virologic cure improve liver and cancer outcomes and survival of patients with various cancers. Chronic HCV is not a contraindication to any cancer regimens but can disrupt liver functions and eventually lead to fibrosis in those on such regimens. Increased HCV replication in cancer patients on immunosuppressive therapy is less common than in HBV. In the DAAs era, it is not acceptable to exclude patients with cancer and chronic HCV infection from oncology trials because of HCV alone; HCV-infected patients facing life-threatening malignancies should have access to investigational

chemotherapy. In summary, overall benefits of DAAs in terms of virologic, hepatic, and oncologic outcomes far outweigh the risks of not treating this curable infection[25].

HCV in chronically transfused patients

Transfusion-dependent patients (*e.g.* Thalassemia) are at a higher risk of acquiring blood borne infections even under conditions of safe transfusion. Since, HCV is one of the most common blood borne pathogen, HCV infection is highly prevalent in children with β-thalassemia major in many countries despite strict pre-transfusion blood testing. This should raise the attention to environmental and community acquired factors. Quality management to insure infection control in minor operative procedures and adding more sensitive tests for blood screening are recommended. Patients with acute HCV and thalassemia have low rates of spontaneous resolution of HCV infection, and the majority develop chronic HCV infection. DAAs combinations are associated with high SVR rates and low adverse events in treatment naïve and experienced patients with chronic HCV and thalassemia. Liver fibrosis is accelerated in thalassemia patients with chronic HCV; therefore, early diagnosis, treatment with DAAs, adequate iron chelation, and non-invasive monitoring of liver status are recommended to prevent development of cirrhosis and HCC[25].

People who inject drugs (PWID)

Currently, the most common mode of transmission for HCV infection in the United States is through IDU; approximately 54% to 77% of new HCV diagnoses are among people who inject drugs (PWID). According to an estimate, 3.5 million people have injected drugs in the United States during their lifetime, with the prevalence of HCV infection in this population projected to be 73% (range 70%-77%). Because of the high probability of contracting HCV infection through needle-sharing, treating PWID infected with HCV, particularly in early stages of the disease, may reduce transmission. Treatment of people who inject drugs (PWIDs) is a top priority because of both the high burden of infection and the potential to transmit to others. The success of treating PWIDs is well established. In the recent SIMPLIFY trial, 103 persons with recent injection drug use (74% injected in the past month) received treatment with SOF-VEL for 12 wk and 94% achieved HCV cure with no virologic failures. Those with prior and current drug use, those on opiate substitution therapy (OST), and those not on OST had similar rates of cure with DAA therapy. Modeling of treatment in populations of PWIDs highlights the need for prevention measures concurrent with HCV treatment[25].

Men who have sex with men (MSM)

Global HCV prevalence in MSM varies by region and HIV status. Behavior counseling and regular HCV monitoring are needed in HIV-positive subgroups and high-risk regions. Given the upward trend of HCV incidence and sexual risk behaviors, there is also a continued need to reinforce risk-reduction intervention. Antiviral therapy along with counselling regarding the disease process regarding a high risk of disease recurrence in these patients is advised. Furthermore, these patients should also be told to incooperate measures that reduce the recurrence of HCV infection. Annual checking with HCV RNA is recommended in these patients who are sexually active[25].

HCV resistance

According to the EASL guidelines of 2020, those patients who were treated with DAAs and had failed to achieve clearance, are advised to be treated *via* a multidisciplinary team and should undergo HCV RNA resistance testing before retreatment. EASL HCV guidelines 2020 also recommend that those patients without cirrhosis or with compensated cirrhosis who failed DAAs regimen should be retreated with SOF/VEL/VOX for a duration of 3 mo. Those who fail to achieve SVR even after treatment with SOF/VEL/VOX, should be administered therapy containing the SOF/GLE/PIB for a period of 24 wk with RBV. Those with decompensated CLD who fail DAAs and with contraindications to the use of DAAs are advised to be treated with SOF/VEL/RBV for 24 wk[25].

HCC

Patients with decompensated cirrhosis who have achieved an SVR after treatment with DAAs are still at high risk of developing HCC due to the advanced stage of cirrhosis. This is due to the oncogenic property of virus itself along with the interaction of viral with the host factors that cause liver cirrhosis to progress towards HCC[32]. This risk increases in obese patients, those co-infected with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV), type 2 diabetes mellitus and HCV genotype [4,32,33]. Kanwal *et al*[34] evaluated Veteran American HCV Clinical Case Registry and documented 80% higher risk of HCC with genotype 3 as compared to genotype 1. Lee *et al*[35] showed that genotype 6 has higher risk association in South Asian population.

On the contrary, various studies have documented that successful viral eradication, established by SVR, is associated with a decreased risk of HCC and decompensation events; hence, reduced HCV-related morbidity and mortality[36,37]. However, in the past, as PegIFN was contraindicated in

decompensated cirrhosis, large cohorts of patients were deprived of treatment benefits[38,39].

Although, treatment with IFN was associated with a low cure rate and higher adverse effects, studies reported that achieving SVR reduced the risk of HCC to 0.5%-1% per annum[40]. The IHIT Study Group also documented decrease in the incidence of HCC in patients with chronic HCV infection treated with IFN and who achieved SVR and biochemical response[41]. Similar response was also documented by Hsu *et al*[42] in Taiwanese population. Moreover, a few studies also demonstrated beneficial response of IFN therapy in patients with cirrhosis and advanced fibrosis but with a lower response[37,43,44].

Although, the favorable response to oral DAAs revolutionized the treatment armamentarium, this development was marred by reports of higher incidence of HCC, HBV reactivation and drug-drug interactions[45-47]. Kanwal *et al*[34] reported cumulative incidence of HCC at 2.8% while Tani *et al*[48] documented 6% at 3 years following treatment with DAAs. However, other studies negated these results. A large prospective observational French cohort documented association of DAAs therapy with decreased all-cause mortality and HCC[49]. Delgado Martínez *et al*[50] reported lower incidence of HCC with DAAs as compared to untreated patients (2.90 and 4.48 per 100 person-years, respectively). Moreover, Romano *et al*[51] reported declining trend in the incidence of HCC among HCV-related cirrhotics treated with DAAs.

A meta-analysis of 41 studies compared recurrence of HCC in patients treated with either DAAs or IFN therapy. The authors demonstrated similar rate of HCC recurrence in patients treated with IFN and DAAs' studies (9.21/100 per year *vs* 12.16/100 per year), respectively[52]. However, Reig *et al*[53] reported higher recurrence of HCC (27.6%) in 5.7 mo of follow-up in 103 DAAs treated patients. Even though, Cabibbo *et al*[54] in a multicenter Italian study reported higher incidence of HCC recurrence in DAAs treated population but concluded that risk is comparable to untreated population. In a recent review by Muzica *et al*[40] the author concluded that incidence of both HCC occurrence and recurrence is significantly reduced by achieving SVR with DAAs.

To summarize, a vast majority of studies support the use of DAAs therapy in patients with advanced liver disease and successfully treated HCC. Whether or not to treat patients with uncured HCC with DAAs is an issue, which still needs to be studied.

RISK OF HBV REACTIVATION

The encouraging response of DAAs in decompensated cirrhosis was refuted by detrimental reports of HBV reactivation. In 2016, FDA had issued black box warning of HBV reactivation based on multiple reports including liver failure and deaths[55]. In HBV-HCV co-infected patients, both HBV and HCV have reciprocal inhibition on each other[56]. In the IFN era, HBV reactivation was a rare occurrence due to its dual antiviral effects on both viruses[57]. In the DAAs era, the reported prevalence of HBV reactivation ranges from 2%-57% in HBsAg-positive while 0%-3% in HBsAg-negative or anti-HBc-positive patients when treated with DAAs[58]. Thus, the pharmacological suppression of HCV with DAAs curbs the inhibitory effect on HBV genome and thus may lead to HBV reactivation[56].

Recently, Mücke *et al*[59] in a meta-analysis reported 24% and 1.4% risk of HBV reactivation in patients with chronic HBV and HBc-total positive patients, respectively. The authors also highlighted that the risk of reactivation was not related to nadir HBV DNA levels or severity of liver disease. Thus, frequent testing and monitoring is required in this population.

AASLD recommends that patients fulfilling treatment criteria for HBV should be treated in patients with co-infection. On the other hand, patients with a low or undetectable HBV DNA levels, can either be treated prophylactically or monitored regularly. Thus, all HCV patients to be treated with DAAs should be tested for HBsAg, anti-HBc total and anti-HBs titer prior to start of DAAs[4].

KIDNEY INVOLVEMENT IN CHRONIC HCV INFECTION

The kidney is involved in chronic HCV infection due to immune complex deposition. Epidemiological studies have documented a high prevalence of chronic kidney disease (CKD) in HCV positive patients [60].

Fabrizi *et al*[61] in a systematic review and meta-analysis documented increased risk of proteinuria and CKD in patients with positive HCV serology. Mendizabal *et al*[62] retrospectively evaluated large database of HCV infected and non-infected population. The authors documented 27% increased risk of CKD in HCV infected compared to non-infected population. Moreover, the risk of CKD reduced by 30% with effective antiviral therapy. Studies have documented rapid renal deterioration from CKD to end-stage renal disease (ESRD). Thus, there is a high rate of morbidity and mortality in HCV-infected CKD patients[63-65].

On the other hand, dialysis patients are at increased risk of acquiring the virus due to poor hygiene, increased risk of nosocomial infection and lack of proper sterilization techniques along with improper handling of equipment. Hence, testing all dialysis patients at entry and periodically thereafter is recommended[66,67]. However, there is some controversy on the type of testing (serology or NAT) in

these patients[68]. These patients have higher prevalence of HCV infection, higher risk of HCC and cirrhosis, and lower survival than the general population[69]. Therefore, withholding HCV treatment till renal transplantation would be detrimental.

During the early era of DAAs, SOF was not recommended in patients with eGFR < 30 mL/min due to the fear that these patients accumulate SOF and its metabolites[70,71]. To address this issue, various authors have experimented with SOF dosage in these patients[72,73] Bhamidimarri *et al*[74] documented virological response with daily 200 mg *vs* alternate 400 mg SOF dose in patients with ≤ 30 mL/min per 1.73 m² of eGFR. However, we documented 96.9% SVR12 in 133 hemodialysis patients treated with SOF-based regimen at daily dose of 400 mg[75]. Moreover, Shehadeh *et al*[76] in a systemic review and meta-analysis reported no statistically significant differences in SVR12 rates amongst dialysis patients treated with 400 mg daily, 400 mg on alternate days or 200 mg daily SOF dose.

A meta-analysis of patients with CKD stage 4 and 5 documented cumulative SVR12 of 89.4% on treatment with SOF-based regimen[77-79]. Borgia *et al*[80] reported SVR12 of 95% among 59 dialysis-dependent patients treated with SOF-VEL combination. In 2019, considering the published safety and efficacy of SOF in advanced CKD patients, Food and Drug Administration (FDA) permitted the use of SOF-based therapy in patients with eGFR ≤ 30 mL/min including dialysis. AASLD also recommended that no dose adjustment is required in this population[4].

Elbasvir/grazoprevir (EBR-GZR) combination was the first to be approved for hemodialysis patients with HCV infection[81]. The efficacy of EBR-GZR for 12 wk was demonstrated in C-SURFER trial in genotype 1 with CKD stage 4 or 5 (eGFR < 30 mL/min). In the immediate treatment group, SVR12 was achieved in 99.1%[82]. The deferred group population were prescribed EBR/GZR combination after 16 wk of trial inclusion (*n* = 99). The authors documented 98% SVR 12 in this group[82]. The study by Bruchfeld *et al*[83] re-inforced the safety and efficacy of EBR/GZR combination in stage 4-5 CKD with HCV genotype 1 infection. AASLD recommends EBR/GZR in genotype 4 infection in stage 4/5 CKD considering encouraging response in general population[4].

EXPEDITION-4 trial assessed pan-genotypic fixed dose combination of GLE-PIB (100/20 mg) in non-cirrhotic stage 4/5 CKD patients. The trial included HCV genotypes 1 to 4 and also treatment-naïve and experienced population. In a total of 104 patients, SVR 12 was achieved in 98% with no virological failures[84]. Subsequently, EXPEDITION-5, a phase 3 trial, evaluated the same fixed dose combination in stage 3b, 4, or 5 CKD in compensated cirrhotic and non-cirrhotic populations. The overall SVR12 was achieved in 97% of the study population[85]. Although trial reported 5% non-serious side effects, Harrison *et al*[86] reported a case of drug- drug interaction with colchicine. Despite 50% reduction of colchicine dose, patient with stage 4 CKD developed rhabdomyolysis and acute kidney injury (AKI) with GLE-PIB combination. The authors recommended withholding colchicine during treatment with NS5A inhibitor containing DAAs, specifically with renal dysfunction. Similarly, Patel *et al*[87] also reported rhabdomyolysis in stage 3 CKD patients secondary to interaction with SOF/LDV, atorvastatin and colchicine use.

In summary, various novel DAAs are highly effective and safe in CKD population. However, drug-drug interactions should be considered in case of use of NS5A inhibitor containing DAAs with P-glycoprotein (P-gp) inducers.

CRYOGLOBULINEMIC GLOMERULONEPHRITIS

Although, HCV can lead to tubulointerstitial nephritis, it is the HCV-associated glomerular disease that is more frequently encountered[81,88]. Nonetheless, its incidence remains fairly low. Other than immune complex deposition in glomeruli, Toll-like receptor 3 has also been postulated to cause renal injury in HCV-infected population[60,89].

Various histological types of HCV-associated renal diseases include cryoglobulinemic membranoproliferative glomerulonephritis (MPGN), mesangial proliferative GN, focal segmental glomerulosclerosis, membranous nephropathy, *etc*[88]. However, the most frequent glomerulopathy is Type I MPGN associated with type II mixed cryoglobulinemia (MC)[60,89]. Around 20% to 56% of patients with HCV-associated MC type II may develop renal involvement[60]. The clinical presentation may vary and nephrotic syndrome, acute nephritic syndrome and oliguric acute renal failure have been reported in 20%, 30% and 5% of patients, respectively[90,91]. In pre-DAAs era, HCV-associated glomerulopathies were treated with IFN. A systematic review and meta-analysis reviewed response of conventional or PegIFN for HCV-associated MC. The kidney involvement was documented in 11%-74% in analyzed 11 studies. The authors reported excellent association of virological response with clinical remission in majority of patients[92]. Similarly, another meta-analysis documented association of virological and clinical response in patients treated with combination of PegIFN and RBV therapy in HCV-infected MC. The kidney involvement in study population ranged from 4% to 39%[93]. Other studies have reported lesser efficacy and more side effects with IFN-based treatment in HCV-MC as compared to HCV-infected general population[94,95]. Moreover, even with > 70% remission with IFN-based therapy in MC-induced vasculitis, the associated adverse effects discourage it use in this population[96].

Although limited, a few studies have documented good response with DAAs. It has also been observed that clinical and immunological response may not correspond to SVR[97-99]. Fabrizi *et al*[88], reviewed 9 clinical studies (*n* = 67) and documented 92% SVR with DAAs though cumulative complete clinical response was low *i.e.*, 38.5%. Furthermore, few case reports have documented new-onset or relapsing glomerular diseases even in patients who achieved SVR with DAAs[100,101].

In view of satisfactory efficacy and lesser side effects, DAAs are advised for viral eradication in patients with HCV-associated MC[88]. Treatment is based on severity of disease involvement. In patients with mild to moderate form of disease (GFR > 30 mL/min/1.73 m² (with or without non-nephrotic proteinuria), DAAs are the first line of treatment. However, immunosuppressive agents (IS) are advised for non-responsive cases or drug intolerance. In patients with cryoglobulinemic flare or severe glomerular injury, IS agents (rituximab) are in the initial treatment algorithm with or without plasma exchange. The resolution of acute phase is followed by HCV treatment with DAAs. However, IS agents and DAAs can be prescribed as per clinicians' discretion[88].

In summary, HCV can be found in 85%-95% of patients with MC[102]. However, only 10%-15% will have clinical manifestations including glomerulopathy[103]. Thus, KDIGO Clinical Practice Guidelines recommend annual evaluation for proteinuria, hematuria and eGFR in HCV-infected population with or without renal dysfunction especially with cryoglobulinemia[104]. The mainstay treatment still remains HCV eradication. Studies have documented encouraging response with DAAs, which, albeit, may lead to partial response[88].

LIVER TRANSPLANT RECIPIENTS

Apart from having a favorable response in the decompensated liver disease, the novel DAAs have led to a paradigm shift in the management of HCV-related disease in the post-transplant setting. In this section, we will highlight the important landmark studies and trials for the treatment of HCV in the solid organ transplant recipients.

During the IFN era, majority of patients with end-stage liver disease were deprived of therapy due to its deleterious side effects or contraindications[105,106]. Hence, HCV positive liver transplant recipients experienced universal liver graft reinfection; consequently leading to poor outcome[107]. However, attainment of SVR post liver transplant was associated with improved survival[108,109].

This scenario has been altered with the advent of DAAs. Cholankeril *et al*[110] in a retrospective study documented 91.9% and 89.8%, one year survival in HCV positive liver recipient transplanted in DAA era *vs* pre-DAA era, respectively. Similarly , Cotter *et al*[111] in a prospectively collected cohort of 18,746 documented statistically significant improved 1 and 3 year post transplant survival in HCV positive recipients in DAA era as compared to past. Among various factors, viral genotype is an important determinant of SVR in post liver transplant recipients[112,113]. Campos-Varela *et al*[112] reported higher risk of advanced fibrosis and lower rate of SVR with PegIFN-based treatment in genotype 1 infected liver transplant recipients. Moreover, the authors also reported statistically significant association of HCV genotypes 2 and 3 with SVR as compared to genotype 1. Similarly, Chen *et al*[114] concurred that HCV genotype 1 was less likely to achieve SVR than non- genotype 1 infection. Zanaga *et al*[115] reported higher SVR with genotype 3 and statistically significant association with SVR on a univariate analysis in post-liver transplant population. A systematic review and a meta-analysis reported pooled SVR12 of 90% with simeprevir (SMV) and SOF combination with or without RBV in recurrent genotype 1 in post liver transplant population. However, interaction with Cyclosporine immunosuppression was also documented[116].

SOF, combined with RBV, was used in 40 liver transplant recipients of all genotypes, and achieved an SVR12 rate of 70% in the study population with no graft loss or rejection. However, no genotype-specific response was documented[117]. Subsequently, the phase 3 ALLY-1 trial documented response of SOF and DAC combination with RBV for 12 wk in liver transplant population with recurrent HCV. Although the study population included treatment-experienced recipients, trial documented 95% and 91% SVR12 in patients with genotype 1 and 3 infections, respectively[118].

SOLAR 1, a phase 2 open label study that was conducted in USA, evaluated the response of LDV and SOF with RBV in 223 liver transplant recipients with HCV genotypes 1 and 4 infections. The study participants were randomly assigned 12 and 24 wk of treatment and achieved SVR12 in 96% and 98%, respectively, without cirrhosis. Moreover, lower rate of SVR12 was achieved in participants with CTP B and CTP C cirrhosis[119]. Similarly, SOLAR 2 trial conducted in Europe, Australia, Canada, and New Zealand also reported higher SVR rate of 93% and 100% in post liver transplant non-cirrhotic recipients treated with LDV/SOF combination with RBV for 12 and 24 wk, respectively. However, amongst recipients with CTP class C cirrhosis, SVR was higher with 24-wk treatment[120].

The use of the first pan-genotypic oral agent, SOF/VEL combination for 12 wk was evaluated in liver transplant recipients with genotypes 1 to 4[121-123]. Considering the beneficial effect of SOF/VEL in decompensated cirrhosis, AASLD, recommends SOF/VEL with RBV combination in liver transplant recipient with decompensated cirrhosis for 12 or 24 wk. Extended treatment is considered for recipients with treatment-experienced genotype 3 infection and presence of HCC[4].

Another pan-genotypic fixed dose single pill combination of GLE-PIB (300/120 mg) is also recommended in transplant recipients[4]. MAGELLAN-2 trial evaluated 100 non-cirrhotic post-transplant patients with or without treatment experience. In intention-to-treat analysis, liver and kidney transplant recipients achieved 97.5% and 100% SVR12, respectively. Although, minor reduction in tacrolimus was required in 1st week but the median dose of cyclosporine, everolimus or sirolimus, remained unchanged[124]. Similarly, SVR12 of 98% with 8 wk or 12 wk of GLE/PIB combination was observed in a multicenter trial of 24 liver transplant patients. Study population also included prior DAAs experience, severe renal impairment, hemodialysis and post-liver transplant jaundice[125].

Although, DAAs are safe and highly efficacious in treatment-naïve and experienced recipients, but in general 5% of the population fails to achieve SVR. This is mostly encountered in recipients with associated decompensated cirrhosis or HCC[126]. Despite lack of published data, on the basis of expert consensus, AASLD recommends SOF/VEL/VOX in patients with DAAs experienced post liver transplant patients[4]. Cardona-Gonzalez *et al*[127] reported successful treatment of recurrent genotype 3 in liver transplant recipients with SOF/VEL/VOX combination in DAAs experienced individuals. Similarly, Higley *et al*[126] recently published a case series of six HCV liver transplant recipients with DAAs failure. The authors documented successful HCV eradication with 12 wk of treatment with no adverse effect or virological relapse during study period.

EASL recommends to initiate DAAs as early as possible after liver transplant once the recipient's clinical condition is stabilized. Generally, it is advised to start treatment after 3 mo of transplant. However, exact time frame for starting DAAs in non-hepatic solid organ transplants has not being recommended. We believe that with widespread availability of new DAAs in pre-transplant period, there will be an increase in the number of DAAs-experienced and/or treatment failure patients among transplant recipients. Thus, pan-genotypic, efficacious and safe salvage therapy is warranted in these special scenarios.

With the increasing availability of liver transplant facilities, the growing demand of donor organs has yet to be met worldwide. Historically, HCV positive donors were only accepted for transplantation in recipients with dire complications like fulminant hepatic failure[128]. However, the recurrence of HCV infection and associated morbidity and mortality were added risks. With the advancements in DAAs, the question of utilizing HCV positive donors was addressed by multiple studies[129]. As compared to renal transplants, data on PCR positive donors to PCR negative liver recipients is limited. However, Cholankeril *et al*[130] and Cotter *et al*[131] reviewed the OPTN registry from 2015 to 2020 and reported comparable 1 and 2-year post transplant survival of patients transplanted with HCV viremic organs, in NAT negative recipients. Bethea *et al*[132] reported 100% SVR in 10 liver recipients who received NAT positive donors treated with 12 wk of GLE/PIB combination. Nonetheless, one recipient developed acute cellular rejection. In a real world experience, Jandovitz *et al*[133] also reported beneficial response of GLE/PIB combination in three HCV negative liver transplant recipients.

RENAL TRANSPLANT RECIPIENTS

HCV-infected renal transplant recipients (RTRs) have a higher survival as compared to being on waiting list despite the complications[134-136]. However, HCV-infected RTRs have reduced graft and patient survival compared to non-infected counterparts. Fabrizi *et al*[137] documented the presence of anti-HCV antibody as a prognostic factor for patient and allograft survival in RTRs with relative risk of 1.79 (95%CI: 1.57-2.03) and 1.56 (95%CI: 1.35-1.80), respectively. An observational meta-analysis reported higher rate of liver- and cardiovascular-related mortality[138]. Although HCV in RTRs leads to slow progression to chronic liver disease (CLD), the increased risk of HCC cannot be disregarded. Long-term immunosuppression is possible culprit to accelerated liver fibrosis; thus, leading to cirrhosis and HCC [139]. Zylberberg *et al*[140] reported significantly higher yearly progression of hepatic necroinflammation and fibrosis in HCV infected as compared to non-infected recipients. Moreover, HCV in RTRs also increases the incidence of infection, glomerulopathy, vasculitis and post-transplant diabetes mellitus[141-144].

In the past, IFN was contraindicated in RTRs due to inferior virological response, low tolerance and increased risk of graft rejection[137,145]. A meta-analysis reported 18% SVR and drop-out rate of 35% in recipients treated with IFN-based regimen[146]. Occasional studies, mostly case reports, documented beneficial response of IFN in renal transplant population[147,148]. Early in DAAs era, SOF was not recommended in patients with eGFR < 30 mL/min due to possible accumulation of SOF and its metabolites causing renal dysfunction[71]. However, various studies have reported favorable response of SOF with RBV in RTRs[149,150]. We have observed 89.2% end-of-treatment response (ETR) and 100% SVR12 in our renal transplant population treated exclusively with SOF and RBV combination. Moreover, we also reported resolution of liver-related ascites in two out of four decompensated recipients[151].

Multiple studies reported 90% to 100% SVR 12 in recipients treated with 2 different class of DAAs [152,153-155]. We also treated our 79 treatment-naive and treatment-experienced RTRs. Majority received SOF and RBV (78.5%) while remaining received SOF, DAC and RBV combination. ETR and

SVR12 were achieved in 98.7% and 96.2%, respectively[151] Coral-1 study evaluated liver and RTRs. The study population including 12 non-cirrhotic RTRs received PrOD with and without RBV in genotype 1a and genotype 1b, respectively. RTRs achieved lower SVR of 75% with premature treatment discontinuation as compared to liver transplant recipients[156]. However, Scott *et al*[157] in a multicenter randomized trial documented 98% SVR 12 in 114 RTRs with genotypes 1 and 4, treated with SOF-LDV for 12 or 24 wk.

A multicenter, prospective observational trial, HCV-TARGET, demonstrated efficacy and safety of SOF-based regimen in transplant population. The cohort included 347, 60 and 50 Liver transplant, kidney transplant and dual liver kidney transplant recipients, respectively. The regimen included SOF-LDV, SOF-DAC and PrOD with or without RBV. In RTRs, trial reported 94.5% SVR12 and acute rejection in two recipients[158]. MAGELLAN-II trial documented safety and efficacy of GLE/GDP combination in liver and kidney transplant population. The population included 20 RTRs with genotypes 1, 3 and 4, among which four were treatment-experienced with IFN-based regimen. The study documented 100% SVR12 with no virological relapse[124]. Long-term follow-up documented by Zhang *et al*[159] reported no virological relapse at 24 and 96 wk post-treatment in eight RTRs treated with SOF-based regimen.

One of the major apprehensions for use of DAAs in transplant population was the drug- drug interaction, thus leading to graft rejection. In a Spanish renal transplant registry, 55.3% of study population required immunosuppression adjustment. Although renal function remained stable during treatment, 2.9% developed acute allograft rejection[160]. Similarly, Scott *et al*[157] reported immunosup-pressive dose alteration in 18% of RTRs treated with SOF-LDV combination. Özer Etik *et al*[149] reported 100% SVR in RTRs but 45% of transplant recipients required increased dose of calcineurin inhibitors. The authors attributed the increased requirement to improved liver function; thus, enhanced drug metabolism. However, various studies did not report immunosuppressive dose modification with SOF-based regimen. AASLD latest guidance recommends not to co-administer cyclosporine with EBR-GZR combination or with GLE/PIB combination. However, Tacrolimus level may need to be adjusted with GLE-PIB combination[4].

Although, multiple studies have documented effective HCV eradication, no graft rejection and stable renal function during and after DAAs therapy[161,162]. Other authors have documented worsening proteinuria in transplant recipients with higher pretreatment levels[155]. Thus, although DAAs are efficacious and safe in RTRs but caution should be practiced with monitoring of calcineurin inhibitor levels, renal functions and proteinuria.

To counteract the shortage of kidney donors, researches have focused on utilizing HCV positive kidneys in HCV negative RTRs[141]. Even with favorable results, the American Transplant Society (ATS) and KDIGO recommend that HCV infected organs can be transplanted into HCV NAT negative recipients as a research protocol only with an informed consent and approval from ethical committee [163,164]. However, KDIGO guidelines recommend HCV NAT-positive kidney to be transplanted to NAT positive recipients with the aim to decrease the organ wastage. Nevertheless, liver fibrosis stage and availability of effective DAAs prior to transplantation should be ensured[163].

Prior to 2000, various studies suggested increased incidence of hepatitis and subsequently poor graft survival in anti-HCV positive kidney recipients transplanted with anti-HCV positive organs[165,166]. Moreover, negative recipients receiving positive donors were associated with higher liver-related complications[167,168]. The effective response to DAAs in post-transplant period had led to address the issue of discarded HCV-positive organs.

To expand the donor pool, researchers have reported response of HCV viremic donors to HCV-negative recipients. The first prospective trial, THINKER-1 in 2017 followed by THINKER-2 in 2018 reported 100% SVR in aviremic RTRs who received NAT-positive organs. All the recipients received EBR/GZR combination for 12 or 16 wk depending on NS5A resistance-associated substitutions (RASs). Although among a total of 20 recipients, two developed proteinuria due to FSGS but all achieved SVR12 [169,170]. Moreover, EXPANDER trial evaluated preemptive treatment regimen in NAT-positive donors to aviremic recipients. All recipients received one dose of EBR/GZR followed by EBR/GZR × 12 wk with or without SOF depending on genotype. In total, 30% of the study population had detectable viremia post-transplant. However, all achieved SVR12[171]. La Hoz *et al*[172] documented no statist-ically significant difference in graft survival and acute cellular rejection (ACR) in aviremic recipients receiving HCV-positive or HCV negative kidney.

Recently, Jandovitz *et al*[133], in a single center prospective study, evaluated the response of GLE-PIB, SOF-LDV and SOF-VEL in 64 RTRs with positive donors and negative recipients. The author reported 95% detectable viremia post-transplant with SVR12 in 41/58 recipients. The result of 17 recipients was awaited at the time of publication. Moreover, two patients developed fibrosing cholestatic hepatitis (FCH), which was successfully treated with DAAs. The study documented 98% patient and graft survival.

HEART AND LUNG TRANSPLANT RECIPIENTS

In the pre-DAAs era, despite the fact that heart and lung tissue are not reservoirs for HCV, utilization of HCV-positive organs was controversial. Studies have reported lower patient survival as compared to recipients with aviremic donors[173,174]. However, the benefits of procedure outweigh the morbidities associated with no transplants in this special group[128].

Abdelbasit *et al*[175] reported first case series of five lung recipients transplanted with viremic lungs. The recipients responded to SOF-based regimen with 100% SVR 12 and 100% patient survival 12 mo after transplant. Recently, Cypel *et al*[176] compared *ex vivo* lung perfusion with or without ultraviolet C radiation (UVC) in 22 NAT-negative lung recipient transplanted with positive donors. In 20 recipients with detectable viremia, 96% achieved SVR12 with SOF/VEL combination. The relapse in two patients including one with FCH was successfully treated with SOF-VEL-VOX and RBV combination.

Similarly, various studies reported beneficial response of DAAs in heart transplant recipients with NAT-positive donors with > 90% SVR12[133,177,178]. Kilic *et al*[179] and Reyentovich *et al*[180] reported no statistically significant differences in 1-year survival in heart recipients transplanted with viremic or aviremic donors. To increase the donor pool, studies have evaluated transplantation of positive donors in NAT-negative recipients, also called HCV aviremic recipients. Bethea *et al*[132] evaluated 20 HCV non-viremic heart recipients treated with first dose of GLE-PIB combination prior to transplantation followed by 8 wk of therapy after transplantation. The author reported 100% SVR12 and 100% graft and patient survival for median of 10.7 mo.

Schlendorf *et al*[181] reported favorable response of SOF-VEL and SOF-LDV in 11 HCV aviremic heart recipients transplanted with HCV-viremic donors. Out of which, nine developed post-transplant viremia, among which eight successfully achieved SVR12. Remaining one recipient was under treatment at the time of publication. Similarly, DONATE HCV trial evaluated the response of four weeks of SOF-VEL combination, started within few hours of transplantation, with NAT-positive donors. The trial included 44 HCV aviremic recipients; 36 underwent lung transplants while eight received heart transplants. Till the time of study publication, 35 recipients achieved SVR12 and reported excellent graft survival at follow-up of six mo[182].

To decrease the risk of infection transmission, trials have been focused on preemptive and shortened DAAs course. Feld *et al*[183] suggested shortest pan-genotypic DAA course in recipients receiving viremic donors. The authors evaluated 30 HCV NAT-negative recipients who received viremic organs which included; 6 hearts, 13 lungs, 10 kidneys and one dual kidney-pancreas. All recipients received one dose of ezetimibe and GLE/PIB followed by only 7 d of treatment course. All recipients achieved SVR12 with genotypes 1-3.

Although, favorable short-term outcomes has been reported for HCV NAT positive and NAT negative donors, the long-term effects of the virus, the infected organs and drug interaction are not known. Hence, during consideration of accepting a HCV viremic donor, the risk of HCV complications including FCH and HCC, insurance policy and availability of pan-genotypic DAAs should be addressed in the informed consent.

FIBROSING CHOLESTATIC HEPATITIS (FCH)

Fibrosing Cholestatic Hepatitis (FCH), a dreaded complication of HCV recurrence, has been described in liver[184,185], renal[186] and heart[187] transplant recipients. It is seen in around 2%–15% of liver transplant recipients and causes significant morbidity and mortality[188,189]. This rapidly progressive disease is characterized by cholestatic jaundice with a high HCV viral load[190,191]. A low threshold of suspicion along with histopathological diagnosis is needed for its prompt management. In pre-DAAs era, despite contraindication in RTRs, KDIGO had recommended IFN in FCH considering the risk-to-benefit ratio. However, this treatment was associated with a low tolerance rate and a poor outcome [141]. The standard of care in transplant population is reduction or withholding immunosuppression followed by anti-viral therapy. Historically treatment with IFN was associated with lower success rate and higher side effects[191,192].

Xue *et al*[193] reported 80% SVR 12 in 10 transplant recipients treated with SOF/RBV combination with PegIFN. The SOLAR 1 and SOLAR 2 trials reported 100% SVR 12 in 6 and 5 transplant recipients, respectively with FCH treated with SOF-LDV and RBV combination[119,120]. Cypel *et al*[176] reported successful treatment of FCH with SOF-VEL-VOX and RBV combination in a lung transplant recipient. Leroy *et al*[194] documented 96% SVR12 in 23 Liver transplant recipients treated with either SOF/RBV or SOF/DAC combination. Moreover, 4 recipients in this study population had concomitant HIV infection. Shinzato *et al*[195] reported a case of post renal transplant FCH treated with GLE/PIB combination. The patient expired due to progressive hepatic failure despite decreased HCV viral load. Jandovitz *et al*[133] reported successful treatment with DAAs in 2 aviremic renal recipients transplanted with HCV-positive donors. Hence, it is proven that the use of DAAs can be beneficial in FCH in post-solid organ transplant recipients.

GLOBAL ERADICATION

From a low virological response to an almost curative treatment for all genotypes, therapy for HCV has evolved markedly in recent years. However, the greatest challenge is yet to be overcome, that is the availability of treatment for everyone. The WHO aims to eliminate viral hepatitis including HCV by 2030 since its poses a major public health threat. In order to implement this, various strategies have been devised to reduce the incidence of viral hepatitis by 90% and decrease liver-related mortality due to these viruses by 65%. To achieve this target, WHO has enlisted five core interventions that need to be focused by all countries globally. These interventions includes vaccination for HBV, prevention of HBV transmission from mother to child, use of screened blood products and safe use of injections, harm reduction in drug users, testing and treatment of HBV and HCV[196]. Despite WHO's support, only a few countries have been able to develop an effective hepatitis control program while even fewer are currently on track to achieve the elimination goal[197]. Egypt, with highest prevalence of chronic HCV infection in the world few years back, conducted a successful HCV screening program that covered more than 50 million people and treated more than 4 million. It is poised to be the first country in the world to eliminate HCV within its borders. The lessons learned from this experience can inform the elimination plans of other LMICs with high HCV burden[198].

Interestingly, DAAs with their high efficacy and short duration of therapy have provided hope on achieving this target but a higher cost of therapy, lack of insurance coverage and un-availability of therapy in many LMICs have become a major obstacle[199]. Some LMICs have heavily subsidized the DAAs for achieving the ambitious goals of HCV elimination. In addition to this, in several countries, effective diagnostic facilities are expensive. Other challenges include inadequate surveillance data, limited coverage of preventive programs and lack of focused leadership to combat HCV menace. However, the major obstacle seen globally is the lack of financial support in hepatitis programs[200,201].

Therefore, there is an urgent need to strengthen the healthcare system and develop a national plan against hepatitis in low-, middle- and even high-income countries. Moreover, support from civil societies, pharmaceutical and medical companies is also required to help the governments of various countries to combat this deadly disease.

CONCLUSION

Significant advances have been made in the fields of diagnostics and therapeutics for optimal management of chronic HCV infection. However, the disease still remains a formidable challenge for all stakeholders, particularly in developing countries. Many hurdles remain to be tackled before the disease is eliminated as envisaged by WHO's goal of eradication of hepatitis by 2030. Concerted and focused global efforts are needed to tackle and eliminate this silent killer effectively.

FOOTNOTES

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